LESIONS OF THE CORTICAL TISSUES INDUCED BY ACUTE EXPERIMENTAL ALCOHOLIC POISONING.[1]

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THE only literature I have been been able to find on the subject of experimental changes in acute alcoholic poisoning is in the incomplete article by Dehio (*Centralblatt f Nervenheilkunde und Psychiatrie*, March, 1895). He rapidly poisoned guinea-pigs with considerable quantities of the drug, the largest amount reaching 25 c.c. of 96% alcohol. Death followed in the most acute case in one hour, in the slowest in thirty-four hours. The method of preparing the microscopic sections was by the Nissl formula. The author confines his research on the cellular changes, entirely to the Purkinje cells, and does not consider the vessels or their contents.

In the cases that died from the poisoning within a very short time, no pathological lesions were found, but in those of longer duration he discovers changes in the chromatin structures of the cell, and greater receptivity of the protoplasm to the stain than is usual, but the nucleus and nucleolus remain unchanged. These very slight lesions of the nerve cell are debatable on the ground that it is impossible with Nissl's method to produce constantly the same degree of staining, also that a definite alteration in the nucleus of a cell is of more positive value than greater or smaller absorption of a dye by the cellular substance. In view of the results obtained from the present research, it is unfortunate that Dehio fails to note whether there were lesions of the blood-vessels' sheaths, or of their contents, for as we already are aware, the soluble poison ricin, is capable of producing decided degenerations of the elements of the vascular walls in much shorter time than thirty-four hours.

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The three rabbits, whose brains were sent me by Dr. Friedenwald for the purposes of this study, were poisoned by a somewhat different procedure than in the foregoing work, namely, by slowly increasing doses of the poison, until the animal had established a certain tolerance, and then increasing it to a considerable amount, which was maintained until the animal died, a method of treatment that does not differ widely from the course pursued by a man on a continual spree. While the doses were large they can hardly be said to greatly exceed the amount taken by many men while on a debauch, and from which they eventually may recover, perhaps after an attack of delirium tremens, or some other form of alcoholic psychosis. Thus a man weighing 150 pounds, would take in the same proportion fifty times the amount of alcohol as a three-pound rabbit, and accordingly, would obtain a daily allowance of 750 c.c. absolute alcohol, equal to about 1,500 c.c. ordinary whiskey, with the difference that the ethyl alcohol is perhaps less deleterious to the tissues.

I insert here a condensed table of the rabbit histories, which shows some interesting facts. The loss of weight in the three animals is enormous. The first case lost approximately three-fifths of its weight, the second seven-twelfths, the third five-ninths; an enormous diminution, considering that the animals were fed and taken care of in the best possible manner, without which they could not live. Another point of note is that the resistance of the animals to the poison is not entirely proportionate to their weight, for the heaviest one received only a total of 165 c.c. of alcohol, and the next heaviest, weighing thirty grammes less, received no less than 260 c.c., nearly one hundred cubic centimetres more before the exitus.

Death occurred in all the cases approximately in three weeks. The principal gross anatomical lesion found at the autopsy was a fatty condition of the heart muscle, and this seems to be present in all animals subjected to continued administration of alcohol, in which sufficient time, between the doses is not allowed for complete elimination.

TABLE OF CONDENSED RABBIT HISTORIES.

ACUTE ALCOHOL SERIES.

No. in Series.	Age.	Weight at beginning of Experiment.	Began to feed 1895.	Quantity fed daily.	Died.	Weight at Death.	Cause of Death.	Gross Anatomical Lesions.	Total Amount of Alcohol fed in three weeks.
E	Adult.	1220 gr.	Sept. 27	5 to 15 c. c.	Oct. 21, 1895	780 gr.	Rapid emaciation. Convulsions.	Fatty Heart	190 c. c.
F	"	1500 gr.	Sept. 30	"	Oct. 21	840 gr.	Rapid emaciation.	"	165 c. c.
G	"	1490 gr.	Oct. 2	"	Oct. 24	920 gr.	Convulsions.	"	260 c. c.

THE MICROSCOPIC EXAMINATION OF THE NERVOUS ELEMENTS AND NEUROGLIA.

The tissues of the brains were hardened in Muller's fluid and absolute alcohol. The staining was accomplished by the Nissl and silver phospho-molybdate methods.

With the aniline stain, alterations are not very definite, beyond a few cells located in the immediate neighborhood of clogged vessels. Here the cellular protoplasm, refuses, under the method, to show its stichochromic structure, and appears uniformly and finely granular, and besides does not take up as much of the dye as other, more normal, cells. In these individual cells there is beginning swelling of the nucleoli, which fill out more than natural of the nuclear ring, and appear slightly roughened. The nuclear dust has not aggregated into clumps, and becomes adherent to the nucleolus, as in some of the more chronic cases seen in the first study.

In the wide areas where the disturbance of the circulation has been less well defined, changes in the protoplasm and nuclei of the cells are not very positive, and show almost entirely, in that the stichochrome particles of the protoplasm are seen somewhat less clearly than normal, and the protoplasm, as an entirety, shows greater receptivity to the aniline stain than is customarily seen in control slides, or better, will not bleach out with the same facility that it ordinarily does. Nucleus and nucleolus appear to be strictly natural. The striated arrangement of the thicker dendrites of the neuron, near the cell body, is always seen.

The silver phospho-molybdate method shows much more positive changes than the Nissl, but these are confined entirely to the dendritic stems beyond the point where they become tinged by the aniline stain. These alterations in the dendrons are not seen everywhere in a section, but at comparatively frequent intervals, corresponding probably to the areas of greatest damage to the circulatory apparatus, for it should be remembered that the smaller vessels are no longer distinctly seen in the silver slides.

The departures from the normal in the dendrons have two forms, swelling of the branches, and apparent atrophy. Dendrons in clusters, in all layers of the cortex, are seen to have irregular tumefactions in the course of their stems, extending over considerable distances in their long diameter, which suddenly decrease to the natural calibre of the stem. The majority of the gemmulae are lost over the extent of these tumefactions, though here and there the buds are found projecting from the sides of the enlargement. Even the branches that have little of the tumefaction, have considerable diminution of the lateral buds. The gemmulae still retained, have lost some of their chief characteristics, the rounded knobs at their terminations are lost, and they show only as even projections from the sides of the protoplasm of the stem of the dendrite. Often, they have a larger than usual size from insertion to termination, which would seem to indicate that they, as a portion of the protoplasm of the dendron, are swollen.

Quite as frequent as tumefaction of the dendrites is a process of apparent atrophy, with almost complete stripping off of the gemmulae from the stems. This diminution of the calibre of the dendrite may be only apparent, and caused solely by the shedding of the side projections, thereby producing an apparent reduction of the calibre of the stem, but varicosities are entirely absent from the dendrites of these neurons.

As far as can be determined, the axons and collaterals are not implicated in the process of degeneration of the dendrites, also no involvement of the cellular body can be found. Some of the corpora, it is true, stained incompletely, but whether this is owing to an imperfect impregnation with the silver salt, or to damage to the protoplasm from the poison and defective circulation, could not be determined.

The dendrons of the Purkinje cells seem to have escaped to a large extent the changes so apparent in the cortex of the cerebrum. Whether this is due to the differences in the circulation of the several regions I am unable to say.

NEUROGLIA.

The number of fixed tissues nuclei stained in the Nissl preparations does not indicate an increase in the numbers of these elements throughout the cortex. In the silver slides the support elements proper, so far as the stain shows, present no variation from the control, but on the other hand the vascular neuroglia gives indication that alterations are taking place within its structures, and show considerable variations from normal preparations. The cell bodies are larger, the protoplasm extensions are thick and knotty, and the arms extending toward neighboring vessels are more prominent than in the control. Altogether the impression is given that these cells are somewhat swollen.

CHANGES IN THE BLOOD-VESSELS SEEN WITH NUCLEAR STAINS.

Arteries and Intermediary Vessels.—The nuclei of the endothelial cells are everywhere swollen, and in places are fragmented, and receive either too little, or more rarely, too much of the dye. The cell substance is also distinctly undergoing retrogressive alterations. The cells of the intermediary vessels look as if they had been subjected to severe strain, as their even contours are distorted, and have many irregular bulges in their outlines.

The change in the muscularis of the arteries is equally interesting. Nuclei are now and then absent from areas of the median wall of the vessel, and in those that remain certain abnormalities are apparent; one-half of a nucleus being occasionally unstained, and presenting the appearance of a vacuole, while in the other portion the chromatin particles take the dye fairly well, and the karyoplasm also receives a portion of the stain. The nuclear membrane surrounding, the entire nucleus is distinct and stained.

But it is in the substance of the muscular protoplasm that the lesions are most apparent, and show that the cells are undergoing a retrogressive process. They no longer have their substance dearly stained, but it is turbid, even hyaline in appearance. The protoplasm, too, is considerably swollen, and its receptive quality to the dye is no longer good, the Virchow-Robin lymph space is entirely obliterated, and in those portions where the tumefaction is most pronounced, there is also almost complete obliteration of the His lymph space, the outer lamina of the vessel being pressed closely against the limiting membrane of the perivascular sheath.

Changes in the adventitia are not so distinct as in the two inner coats, though in places it holds considerable numbers of leucocytes. Some are found lying packed between the adventitia and the outer wall of the lymph space. These elements are swollen and necrotic.

The contents of the perivascular spaces, where the degree of compression is insufficient to obliterate them, is instructive. There are large numbers of leucocytes in various stages of degeneration, and besides there is frequently a number of large protoplasmic bodies, several times the size of a polynuclear leucocyte, very granular, and without nucleus, that probably are formed from the remains of partially broken up lymphoid corpuscles, that have aggregated into crescentic or oval forms. Besides these bodies there is a quantity of detritis, finely granular in character, not sufficient to cause without the aid of the lymphoid cells, any blocking of the nutrient currents. Osmic acid produces a slight blackening of the degenerating white corpuscles, also of the detritus within the spaces.

The capillaries, like the intermediary vessels are tortuous and twisted, their nuclei show changes similar to those in the larger vessels, the cells have departures from the normal in staining, and here and there in the lumen are plugs of white blood corpuscles, which, from their closely packed appearance, must have entirely stopped the circulation of the blood in the vessels before death. The lumen beyond the plugs is entirely empty.

Veins.—Changes in the coats of these vessels are similar to those in the arterial system, but aggregations of dying polynuclear corpuscles are more frequent, and are by far the most striking feature both of their contents and surroundings.

These aggregations, which may vary from three or four, to a dozen or more, are located both within and without the lumen of the vessel (especially the smaller ones). Within the lumen are collections of white corpuscles filling the interior, and numbers are seen penetrating the walls. So numerous are the collections in the peri-venous spaces that the whole cavity is occasionally filled, and backward pressure from the plugs and compression of the vessel from the outside has attained such a height, that in a number of instances the vessel's walls have ruptured, and red corpuscles are intermingled with the white and fill the space completely. In one instance the site of the rupture was located in the section. All the leucocytes, within and without the vessels, show more or less evidence of degeneration, in some extending to erosion and disintegration of the cells.

The individual arteries, particularly the medium sized ones, are quite differently affected by the morbid process, some showing lesions of a character much more advanced than others. This would appear to depend largely upon the numbers of lymphoidal plugs, both in the smallest arteries and capillaries, for where they are thickly scattered, there the amount of arterial degeneration is greatest, particularly the lesions of the muscularis. It would thus appear that at some period antedating the death of the animals, that collections of leucocytes formed in the smaller vessels and veins, and a slowly increasing backward pressure upon the arteries began, not sufficient, it is true, to occasion complete stasis, but enough to create an unusual pressure upon them, and this pressure in combination with the poisonous effects of the alcohol carried with the nutrient fluids, caused degeneratien of the cellular elements forming the blood vessel's walls, the stress of the action falling upon the inner coats of the arteries.

This severely increased pressure is probably only an exaggeration of what ordinarily follows the administration of a moderate amount of alcohol to an animal. There soon follows the ingestion, a dilatation of all the arteries of the body from the paralyzing action of the drug on the vaso-constrictor nerves, and this endures a variable time, according to the quantity of alcohol taken. But the apparent fact that the gray substance of the cerebrum has a different innervation for its arteries than other portions of the body, becomes in this instance, a factor of great importance. Vascular nerves may be found without trouble or difficulty in muscles, glands, etc., by the silver and other stains, but in the substance of the encephalon they are never to be seen with similar staining methods; hence it is fairly reasonable to suppose that they are not present in this location, and that some other controling mechanism takes their place. I have most carefully looked for them in many brains, both human and of the lower animals, but have never seen the slightest traces of their presence within the nervous structures. They are to be readily found in the soft meninges of the brain and in the choroid plexuses, but nowhere within the proper substance of the cerebrum. Tuke and Andriezen, who have made researches in the same field, have also failed to find them.

The mechanism controling the cortical arteries, is therefore, presumably, different from that in other portions of the body, and the muscular cells are less directly under the influence of nerve control. What is the result when we have a stimulant administered? The muscular cells under the influence of the direct action of the poison, and free from any power to urge them to contract after the immediate effect of the toxic substance has passed, remain for a long time inert, the congestion of the cerebral tissues is long continued, larger amounts of poisoned blood pass through the brain, and incidentally a greater proportion of alcohol than to other tissues, the deteriorated serum is transuded in increased quantities, it is carried into the lymph spaces surrounding the cerebral cells, their structures are bathed in the diluted alcohol, and their activity is dulled by the narcotic, weakened as it is by the serous fluid, inertia and torpor, of the functional activities of the cells, is the result, and it is only after the long continued elimination of the poison from the system that they resume their normal functions.

If the quantity of the poison to which the tissues are subjected is very considerable, and continued from day to day, and the emunctories become clogged for a long time, the damage to the vascular wall is proportionately greater. Judging from the present cases, the damage may proceed to necrotic changes in the endothelial and muscular cells; leucocytes formed in other portions of the body accumulate in the cerebral vessels, from the increased amount of blood brought by the arteries not being carried off promptly by the venous system, therefore, we have a constant accumulation of these corpuscular elements, terminating finally in blocking of the capillaries and smaller veins, diapedesis, choking up of the perivascular lymphatic channels, finally clogging of the lymph flow, and eventual damage both to the walls of the arteries by backward pressure acting on a tissue already prone to undergo degenerative changes from the deleterious effects of a poisonous drug, and to the veins from abundant extravasations and transudations of the corpuscular cells.

In conclusion, the large dependence of the lesions of the nerve elements upon the vascular is very readily demonstrated in the Nissl slides by all the alterations of importance being in the neighborhood of damaged vessels, while those supplied by a more steady current of nutrient fluid show only uncertain departures from the normal in their chromatin. It is hardly necessary to add that these latter lesions, though slight, are but the precursors of deeper degenerations of the protoplasm, which eventually show in the nuclear alterations of the more chronic cases. It would appear as an interpretation of the significance of the silver preparations that considerable destruction may take place in the dendritic stems from the combined effects of the alcohol and the damage to the nutrient supply, and that these lesions may be present in the advanced degree, before any implication of the corpus with its inner structures, is discoverable.

The lesions of the blood-vessels and their contents are pre-eminently the most important facts established by this study. We have in some measure already advanced the theory that changes in the constituent elements of the blood are among the first alterations produced by the poisonous effects of alcohol on the blood-forming organs, in other words alcohol has a decidedly disturbing influence on the blood formation. This is in conformity with what is seen in the clinic, and may at some future time form the basis of an interesting blood investigation. The exceeding abundance of the polynuclear leucocytes in and around the cerebral vessels of the rabbits show that there is most probably excessive production of these elements, but we know nothing of the numbers of the red corpuscles, though in all likelihood, there is the same diminution as in so many other anaemic states.

The formation of the many thrombotic plugs of lymphoidal elements is very remarkable and interesting, as are also the numerous transudations of these corpuscles through the vascular walls, indeed so numerous were they in some instances that they compressed the sheaths of the small intermediary vessels and practically closed them.

The study has shown what has never before been demonstrated, that poisoning with alcohol in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum, very similar in character to the pathological lesions produced by other more virulent soluble poisons. One point should be borne in mind between this study and a similar one upon the human alcoholic brain, that man has through long generations been accustomed to the use, or abuse of alcohol, in some form, and has established a certain degree of tolerance to the drug, and therefore the poisonous effects will be less pronounced than in animals that have established no hereditary tolerance.